Clinical Compliance in Personalised Model-based Medical Decision Support: Do computers and interfaces yield better compliance?

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Abstract: Personalised and model-based clinical care is on the rise and offers significant opportunity to improve care and productivity in response to rising demographic demands and rising costs. Compliance in critical care is important for any protocolised clinical care. However, it is often overlooked and very infrequently studied. Critically ill patients often experience stress-induced hyperglycemia, which has been shown to result in increased morbidity and mortality. Safe, effective glycemic control (GC) can reduce mortality and improve outcomes, but is only effective if strong compliance is observed within the clinical practice. This study examines insulin-nutrition dosing compliance for STAR, a tablet-based protocol designed to easily adapt to variable clinical practice, its neonatal intensive care unit version GRYPHON, and a standard paper based clinical protocol (CHU). All interventions and changes were recorded for all three cohorts, and a sub-cohort was used to examine the validity of the data used. Compliance was over 99% for STAR, over 98% for GRYPHON and 80% for CHU. The differences is attributed primarily to interface design and its focus on ease of use and natural use for clinical staff. However, while compliance is higher, the reasons for good compliance in any such system remains to be more precisely specified with appropriate research tests.

Keywords: Model-based, Glycemic Control, Decision Support, Compliance, Intensive Care, Critical Care, Model-based Therapeutics, ICU.

1. INTRODUCTION

Hypoglycaemia, hyperglycaemia, and blood glucose (BG) variability are associated with higher mortality and worsened outcomes in critical care units (ICU), including severe infection, sepsis and septic shock, myocardial infarction, and multiple organ failure (McCowen et al., 2001, Capes et al., 2000, Krinsley, 2003, Krinsley, 2009, Bagshaw et al., 2009, Van den Berghe et al., 2006a). Early studies showed benefits from intensive insulin therapy in the ICU (Van den Berghe et al., 2001a, Van den Berghe et al., 2003, Krinsley, 2004, Chase et al., 2008b), with improved outcomes (Chase et al., 2010, Van den Berghe et al., 2003), reduced mortality, and reduction of patient length of stay and nurse workload (Krinsley, 2005, Van den Berghe et al., 2006b). However, more recent trials have failed to reproduce these results, and have shown higher risks of hypoglycaemia (Griesdale et al., 2009, Wiener et al., 2008, Preiser et al., 2009, Finfer et al., 2009).

One explanation for these conflicting results is the role of increased hypoglycaemia and BG variability in confounding results (Bagshaw et al., 2009, Egi et al., 2010, Penning et al., 2014a, Krinsley et al., 2015). To adequately test the improved outcome hypothesis, insulin therapy must be carried out in a safe and effective manner, and be consistently achieved for all or nearly all patients (Chase et al., 2010). In addition, glycaemic control protocols must effectively manage metabolic variability, which drives glycaemic outcome (Chase et al., 2011c). Thus, fixed table-based or *ad hoc* protocols, often used in hospital ICUs, lack patient specificity and rely on clinical judgement, often failing to account for such variability.

STAR (Stochastic TARgeted) is a clinically validated model-based glycaemic control framework (Evans et al., 2012, Fisk et al., 2012, Stewart et al., 2016). It uses model-based insulin sensitivity to characterise and forward predict changes in metabolic state. Insulin and nutrition treatments are selected such that forward predictions of likely BG outcomes are within the target range, and the treatment does not exceed a 5% likelihood of BG $\leq$ 4.0 mmol/L. STAR has delivered virtually identical glycemic control in very different ICUs in ICUs in the Christchurch, New Zealand, and Gyula, Hungary, demonstrating its strong ability to generalise across patients and units, which no other clinical protocol has been able to do to date (Stewart et al., 2016).

Thus, one major lesson to date is model-based, personalised glycemic control has proven much more capable than clinical, ad-hoc methods in providing quality control. This outcome has been shown with STAR and a few other protocols (Stewart et al., 2016, Blaha et al., 2016). However, the original, very successful Leuven protocol from the original study by van den Berghe et al was not only very successful (Van den Berghe et al., 2001b), but outperformed a very good model-based system (Dubois et al., 2017).

The main question is thus what limited the clinical protocols from achieving these outcomes?

Workload is one factor (Mackenzie et al., 2005, Aragon, 2006). The inability to personalise care and create "one method fits all" approaches instead of "one size fits all" plays a major role (Chase et al., 2011a, Chase et al., 2011b), as many clinical protocols are not able to provide good control, unlike the Leuven protocol.

This analysis leaves protocol compliance as a potential major, often overlooked source of variability. The NICE-SUGAR trial showed negative results, but had non-compliance rates up to 50% or more in an independent analysis (Uyttendaele et al., 2017b), as they did not monitor compliance (Finfer et al., 2009). Hence, non-compliance impacts performance, safety and thus outcomes (Uyttendaele et al., 2017a).

This study analyses compliance for a computerised model-based protocol, STAR (Stewart et al., 2016), a widely used neonatal ICU (NICU) version (GRYPHON) (Alsweiler et al., 2017, Dickson et al., 2018), and a clinical protocol from a third ICU. It thus assesses the impact of computer interfaces on clinical complisance.

2. METHODS

2.1 Protocols:

Three protocols are examined:

1. STAR (Stewart et al., 2016): as used in the adult ICU in Christchurch, New Zealand as a standard of care since 2011.
2. GRYPHON (Dickson et al., 2018): as used in the Christchurch Women's Hospital, Christchurch, New Zealand as a standard of care since 2010
3. CHU (Dickson et al., 2017): a clinical protocol used in CHU de Liege, Belgium since 2013

STAR and GRYPHON are model-based and personalised and model predictive. They represent the emerging mix of computation and health care. Both provide performance well above reported clinical studies. CHU provides relatively good control and a computer-free clinical protocol comparator.

STAR and GRYPHON directly save all clinical and intervention dose data on tablets. CHU data was recorded directly from patient data sheets. All data and anonymised use was approved by the NZ National Ethics Committee (STAR and GRYPHON) and the Ethics Committee of the Medical Faculty of the University of Liege, Belgium (CHU).

2.2 Compliance and Analyses:

Compliance is defined as not changing the recommended dose. Every BG measure, as specified by a protocol leads to another intervention. Where a recommendation is changed, it is counted as non-compliance. It is recorded per-patient. Each patient has a compliance value for each type of intervention (insulin, nutrition). Results are reported as mean compliance across the entire cohort for each protocol and intervention.

STAR modulates both insulin and nutrition. It gives insulin in either bolus or infusion, yielding three values. GRYPHON modulates only insulin, leaving nutrition to clinical standards, so there is only one compliance value. CHU controls insulin only and leaves nutrition to local guidelines. Performance has been reported elsewhere for all 3 cases (Dickson et al., 2018, Dickson et al., 2017, Stewart et al., 2016).

A sub-analysis is run for STAR, which has the most clinical data and patients. It examines 23 patients (~10% of patients and hours). It compares compliance on the tablet to data on bedside charts. Note the STAR sub-cohort was statistically similar to the STAR cohort in Age, Sex, and length of stay, % surgical, APACHE II score, and glycemic control. This analysis assesses if nurses were "honest" with the STAR tablet system and if compliance varies in an unknown way.

Glycemic control performance for each protocol was similar to all reports referenced. It is not reported as each targets different bands and has different approaches. Hence, the study considers only compliance to protocol recommendation in this analysis. Results are reported as median [IQR =inter-quartile range] across the cohort and compared using Mann-Whitney tests and $p < 0.05$ is considered significant.

Overall, this study assesses compliance for two model-based and one clinical protocol. It validates the model-based cases based on a test comparison to a sub-cohort of patients to ensure compliance reported by tablet software is as reported on the official bedside medical charts. The goal is to assess compliance and the impact of computers and interfaces.

3. RESULTS

Table 1 reports mean compliance for all protocols. STAR and GRYPHON have very high compliance over 95%. CHU has relatively high compliance of 80%, but this value is still much lower than the model-based systems with personalised, model-based control even though it is higher than some clinical reports and analyses with ~50% compliance. Table 2 compares STAR and the STAR sub-cohort. The results show there is no clinically or statistically significant differences in results between using the tablet reported data and direct examination of the bedside charts, despite searching for likely cases. It is thus a worst case analysis.

Table 1: Mean recommendation compliance in percent

	STAR	GRYPHON	CHU
#Patients	258	35	20
#Hours	20692	3180	5006
# BG	11180	886	1391
Insulin Bolus	99.6%	NA	NA
Insulin Infusion	99.5%	95.6%	80.8%
Nutrition Rate	96.8%	NA	NA

Overall, the results in Table 2 validate the overall analysis from the tablet computer data. It is worth noting again that

the cohorts were also statistically similar. In addition, GRYPHON is a similar system and approach to STAR, and is used in the same two hospital setting in Christchurch, so the results are assumed to hold for this case, as well.

Table 2: STAR vs STAR Sub-Cohort compliance analysis

	STAR	STAR Sub-Cohort	P-value
#Patients	258	23	
#Hours	20692	1704	
# BG	11180	921	
Ins Bolus	98.1 [94.1: 100.0]	100.0 [96.6 : 100.0]	0.16
Ins Infusin	100.0 [100.0: 100.0]	100.0 [100.0: 100.0]	0.96
EN Rate	96.6 [90.9: 100.0]	98.2 [93.6 : 100.0	0.44
PN Rate	98.2 [92.4: 100.0]	100.0 [99.2 : 100.0]	0.17

4. DISCUSSION

Table 1 shows while CHU had good compliance compared to many protocols at 80% (Uyttendaele et al., 2017b, Mackenzie et al., 2005, Anger et al., 2006, Rood et al., 2005), it is well below the 96.8-99.6% for STAR and GRYHON. These outcomes match other studies showing improved compliance with computerised protocols, model-based or otherwise (Anger et al., 2006, Mann et al., 2011, Morris et al., 2008, Rood et al., 2005). The results show the impact of human factors, where paper-based clinical protocols are potentially harder to use (Carayon et al., 2014, Chase et al., 2008a).

Equally, a computer interface, regardless of algorithm efficacy, can deliberately offer better design for use. This design for human factors was deliberte for STAR (Ward et al., 2012) and GRYPHON. In addition, it can be used to reduce errors in numerical calculation or recording (Ward et al., 2012), which have up to 10% of incidence (Campion et al., 2010). Thus, well-designed computer interfaces offer potentially improved compliance and error reduction.

Table 2 sub-cohort analysis shows Christchurch staff were highly compliant and validates the tablet data was accurate to the true record on bedside charts. This validation comparison is a worst case analysis because the sub-cohort cases were selected for "suspicious behaviour" deviating from typical profiles of therapeutic dosing.

GRYPHON is assumed to have similar compliance as STAR based on 2 main points. First, Christchurch Women's Hospital is next to Christchurch Hospital and shares overall clinical and hospital culture. Second, the GRYPHON and STAR interface designs are very similar, sharing all major details, with only minor differences due to cohort. However, it remains to be verified. CHU data was recorded from the bedside chart data and is thus the "truest" data available.

Finally, while clinical staff could be untruthful about what they record on the patient bedsheet, it is a major offence and very unlikely. Thus, the comparison to bedside chart data is as close to a gold standard truth as possible. In future, as devices become more integrated via the internet of things (IoT) (Whitmore et al., 2015) these data will be able to be cross checked. This future is increasingly likely as seen in the growth of cloud and web-based data services in medicine.

There are limitations to this study. First, there is only a single clinical protocol (CHU). Clinical protocols and their ease of use, and thus compliance can vary significantly (Chase et al., 2008a). The factors that lead to non-compliance are thus very varied and not always easily explained.

For example, a main area of compliance comes from trust in the protocol (Chase et al., 2008a). Trust in a clinical setting arises typically from safety and performance, particularly in glycemic control where poor control has negative outcomes (Finfer et al., 2012, Krinsley, 2008, Krinsley et al., 2011, Krinsley, 2003) and good control has positive impact (Krinsley et al., 2015, Signal et al., 2012). Thus, it may not be possible to separate the quality of the protocol and its glycemic control, and the compliance seen. There is not yet a study comparing compliance in two protocols using the same interface, though one is ongoing (Alsweiler et al., 2017).

Trust is also a factor that is gained with increasing confidence in a system due to observed positive results and repeated use and support. Thus pilot trials are essential to the implementation of a new "smart" or computer-based protocol, where clinical staff have the opportunity to closely observe outcomes. However, it is worth noting that for these pilot trials, compliance must be insisted upon and enforced where clinically reasonable, otherwise new applications are undermined before they are even able to prove themselves.

Finally, it has been observed that non-compliance in the protocols shown here are due in part to caution (Penning et al., 2012, Penning et al., 2014b). This outcome supports the prior discussion, where in this case nursing staff reduce insulin dosing for fear of hypoglycemia and its negative impact on outcome. It thus suggests that compliance will vary with trust, exposure and training/experience, which remains to be verified in an appropriate test or trial.

However, it was also noted nursing staff used to clinical protocols often consider varying the dose. In particular, nurses reported they varied doses to manage patient variability, which defines glycemic control and its difficulty in these cohorts (Chase et al., 2011b, Pretty et al., 2012). More specifically, they manage patient variability by deliberately varying from the overall clinical protocol.

In contrast, personalised model-based methods, such as STAR and GRYPHON, manage variability directly. Where STAR and GRYPHON are successful in building trust around clinical compliance is they seek to communicate how variability is managed and accounted for. Figure 1 shows an interface screenshot, where clinical staff are offered several options for treatments, which they are free to select based on

their own clinical equipoise. Their decision making process is assisted by the graph, which shows the 90% likelihood range of possible glycaemic outcomes for each treatment. Thus, STAR and GRYPHON show the reasoning for the treatments offered, even as each treatment arises from complex simulation. Clinical feedback indicate such graphs supporting treatment options aid clinical staff in their decision making process, by increasing understanding of treatment choices.

Thus, any transition into cyber-physical systems mixing clinical care with significant computation must directly consider clinical equipoise and the communication of how direct management of variability is achieve in the training delivered. This will likely also involve end-used consultation with interface design to ensure the most natural transition and thus, potentially, the best compliance. Again, these conclusions remain to be tested directly.

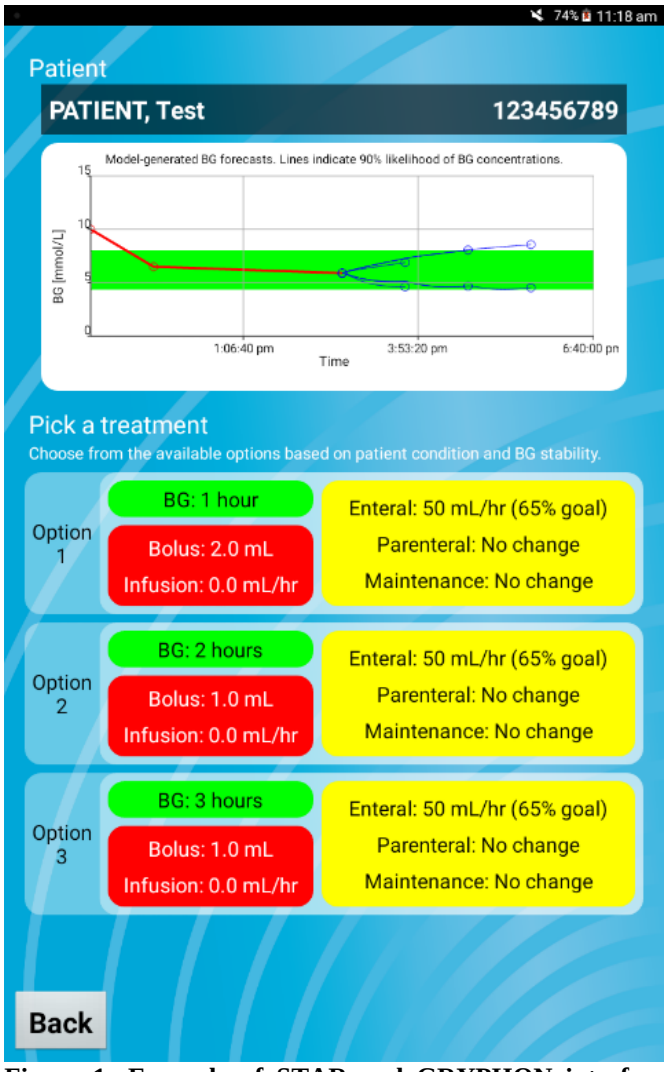

Figure 1: Example of STAR and GRYPHON interface design for clinical decision support.

5. CONCLUSIONS

Personalised and model-based clinical care is on the rise and offers significant opportunity to improve care and productivity in response to rising demographic demands and rising costs. Compliance in critical care is important for any protocolised clinical care. However, it is often overlooked and very infrequently studied.

This study compared compliance of two personalised and model-based decision support systems for glycemic control in critical care with a typical sliding scale styled paper protocol. Compliance was 25% higher (relatively, 18-19% absolute) for the model-based decision support systems, even though the clinical protocol had compliance far higher than seen in some other studies with similar protocols. The differences is attributed primarily to interface design and its focus on ease of use and natural use for clinical staff. However, while compliance is higher, the reasons for good compliance in any such system remains to be more precisely specified with appropriate tests.

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REFERENCES

ALSWEILER, J., WILLIAMSON, K., BLOOMFIELD, F., CHASE, G. & HARDING, J. 2017. Computer-determined dosage of insulin in the management of neonatal hyperglycaemia (HINT2): protocol of a randomised controlled trial. *BMJ Open*, 7**,** e012982.

ANGER, K. E. & SZUMITA, P. M. 2006. Barriers to glucose control in the intensive care unit. *Pharmacotherapy*, 26**,** 214-28.

ARAGON, D. 2006. Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. *Am J Crit Care*, 15**,** 370-7.

BAGSHAW, S. M., BELLOMO, R., JACKA, M. J., EGI, M., HART, G. K., GEORGE, C. & COMMITTEE, A. C. M. 2009. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Crit Care*, 13**,** R91.

BLAHA, J., BARTECZKO-GRAJEK, B., BEREZOWICZ, P., CHARVAT, J., CHVOJKA, J., GRAU, T., HOLMGREN, J., JASCHINSKI, U., KOPECKY, P., MANAK, J., MOEHL, M., PADDLE, J., PASCULLI, M., PETERSSON, J., PETROS, S., RADRIZZANI, D., SINGH, V. & STARKOPF, J. 2016. Space GlucoseControl system for blood glucose control in intensive care patients--a European multicentre observational study. *BMC Anesthesiol*, 16**,** 8.

CAMPION, T. R., JR., MAY, A. K., WAITMAN, L. R., OZDAS, A. & GADD, C. S. 2010. Effects of blood glucose transcription mismatches on a computer-based intensive insulin therapy protocol. *Intensive Care Med*, 36**,** 1566-70.

CAPES, S. E., HUNT, D., MALMBERG, K. & GERSTEIN, H. C. 2000. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and

without diabetes: a systematic overview. *Lancet,* 355**,** 773-778.

CARAYON, P., WETTERNECK, T. B., RIVERA-RODRIGUEZ, A. J., HUNDT, A. S., HOONAKKER, P., HOLDEN, R. & GURSES, A. P. 2014. Human factors systems approach to healthcare quality and patient safety. *Appl Ergon,* 45**,** 14-25.

CHASE, J., ANDREASSEN, S., JENSEN, K. & SHAW, G. 2008a. The Impact of Human Factors on Clinical Protocol Performance - A proposed assessment framework and case examples. *Journal of Diabetes Science and Technology (JoDST),* 2**,** 409-416.

CHASE, J. G., LE COMPTE, A. J., PREISER, J. C., SHAW, G. M., PENNING, S. & DESAIVE, T. 2011a. Physiological modeling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice? *Ann Intensive Care,* 1**,** 11.

CHASE, J. G., LE COMPTE, A. J., SUHAIMI, F., SHAW, G. M., LYNN, A., LIN, J., PRETTY, C. G., RAZAK, N., PARENTE, J. D. & HANN, C. E. 2011b. Tight glycemic control in critical care-The leading role of insulin sensitivity and patient variability: A review and model-based analysis. *Computer Methods and Programs in Biomedicine,* 102**,** 156-171.

CHASE, J. G., LE COMPTE, A. J., SUHAIMI, F., SHAW, G. M., LYNN, A., LIN, J., PRETTY, C. G., RAZAK, N., PARENTE, J. D., HANN, C. E., PREISER, J. C. & DESAIVE, T. 2011c. Tight glycemic control in critical care--the leading role of insulin sensitivity and patient variability: a review and model-based analysis. *Comput Methods Programs Biomed,* 102**,** 156-71.

CHASE, J. G., PRETTY, C. G., PFEIFER, L., SHAW, G. M., PREISER, J. C., LE COMPTE, A. J., LIN, J., HEWETT, D., MOORHEAD, K. T. & DESAIVE, T. 2010. Organ failure and tight glycemic control in the SPRINT study. *Crit Care,* 14**,** R154.

CHASE, J. G., SHAW, G., LE COMPTE, A., LONERGAN, T., WILLACY, M., WONG, X. W., LIN, J., LOTZ, T., LEE, D. & HANN, C. 2008b. Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. *Crit Care,* 12**,** R49.

DICKSON, J. L., LYNN, A., SHAW, G. M. & CHASE, J. G. 2018. Safe and Effective glycaemic control in premature infants: observational clinical results from the computerised STAR-GRYPHON protocol. *Archives of disease in childhood,* in-press**,** 8-pages.

DICKSON, J. L., STEWART, K. W., PRETTY, C. G., FLECHET, M., DESAIVE, T., PENNING, S., LAMBERMONT, B. C., BENYO, B., SHAW, G. M. & CHASE, G. 2017. Generalisability of a Virtual Trials Method for Glycaemic Control in Intensive Care. *IEEE Trans Biomed Eng*.

DUBOIS, J., VAN HERPE, T., VAN HOOIJDONK, R. T., WOUTERS, R., COART, D., WOUTERS, P., VAN ASSCHE, A., VERAGHTERT, G., DE MOOR, B., WAUTERS, J., WILMER, A., SCHULTZ, M. J., VAN DEN BERGHE, G. & MESOTTEN, D. 2017. Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial. *Crit Care,* 21**,** 212.

EGI, M., BELLOMO, R., STACHOWSKI, E., FRENCH, C. J., HART, G. K., TAORI, G., HEGARTY, C. & BAILEY, M. 2010. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc,* 85**,** 217-24.

EVANS, A., LE COMPTE, A., TAN, C. S., WARD, L., STEEL, J., PRETTY, C. G., PENNING, S., SUHAIMI, F., SHAW, G. M., DESAIVE, T. & CHASE, J. G. 2012. Stochastic targeted (STAR) glycemic control: design, safety, and performance. *J Diabetes Sci Technol,* 6**,** 102-15.

FINFER, S., CHITTOCK, D. R., SU, S. Y., BLAIR, D., FOSTER, D., DHINGRA, V., BELLOMO, R., COOK, D., DODEK, P., HENDERSON, W. R., HEBERT, P. C., HERITIER, S., HEYLAND, D. K., MCARTHUR, C., MCDONALD, E., MITCHELL, I., MYBURGH, J. A., NORTON, R., POTTER, J., ROBINSON, B. G. & RONCO, J. J. 2009. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med,* 360**,** 1283-97.

FINFER, S., LIU, B., CHITTOCK, D. R., NORTON, R., MYBURGH, J. A., MCARTHUR, C., MITCHELL, I., FOSTER, D., DHINGRA, V., HENDERSON, W. R., RONCO, J. J., BELLOMO, R., COOK, D., MCDONALD, E., DODEK, P., HEBERT, P. C., HEYLAND, D. K. & ROBINSON, B. G. 2012. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med,* 367**,** 1108-18.

FISK, L. M., LE COMPTE, A. J., SHAW, G. M., PENNING, S., DESAIVE, T. & CHASE, J. G. 2012. STAR development and protocol comparison. *IEEE Trans Biomed Eng,* 59**,** 3357-64.

GRIESDALE, D. E., DE SOUZA, R. J., VAN DAM, R. M., HEYLAND, D. K., COOK, D. J., MALHOTRA, A., DHALIWAL, R., HENDERSON, W. R., CHITTOCK, D. R., FINFER, S. & TALMOR, D. 2009. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ,* 180**,** 821-827.

KRINSLEY, J. 2005. Glucose control reduces ICU stay and mortality. *Perform Improv Advis,* 9**,** 4-6, 1.

KRINSLEY, J., SCHULTZ, M. J., SPRONK, P. E., VAN BRAAM HOUCKGEEST, F., VAN DER SLUIJS, J. P., MELOT, C. & PREISER, J. C. 2011. Mild hypoglycemia is strongly associated with increased intensive care unit length of stay. *Ann Intensive Care,* 1**,** 49.

KRINSLEY, J. S. 2003. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc,* 78**,** 1471-1478.

KRINSLEY, J. S. 2004. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc,* 79**,** 992-1000.

KRINSLEY, J. S. 2008. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med,* 36**,** 3008-13.

KRINSLEY, J. S. 2009. Glycemic variability and mortality in critically ill patients: the impact of diabetes. *J Diabetes Sci Technol,* 3**,** 1292-301.

KRINSLEY, J. S. & PREISER, J. C. 2015. Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults. *Crit Care,* 19**,** 179.

MACKENZIE, I., INGLE, S., ZAIDI, S. & BUCZASKI, S. 2005. Tight glycaemic control: a survey of intensive care practice in large English hospitals. *Intensive Care Med,* 31**,** 1136.

MANN, E. A., JONES, J. A., WOLF, S. E. & WADE, C. E. 2011. Computer decision support software safely improves glycemic control in the burn intensive care unit: a randomized controlled clinical study. *J Burn Care Res,* 32**,** 246-55.

MCCOWEN, K. C., MALHOTRA, A. & BISTRIAN, B. R. 2001. Stress-induced hyperglycemia. *Crit Care Clin,* 17**,** 107-124.

MORRIS, A. H., ORME, J., JR., TRUWIT, J. D., STEINGRUB, J., GRISSOM, C., LEE, K. H., LI, G. L., THOMPSON, B. T., BROWER, R., TIDSWELL, M., BERNARD, G. R., SORENSON, D., SWARD, K., ZHENG, H., SCHOENFELD, D. & WARNER, H. 2008. A replicable method for blood glucose control in critically Ill patients. *Crit Care Med,* 36**,** 1787-95.

PENNING, S., CHASE, J. G., PREISER, J. C., PRETTY, C. G., SIGNAL, M., MELOT, C. & DESAIVE, T. 2014a. Does the achievement of an intermediate glycemic target reduce organ failure and mortality? A post hoc analysis of the Glucontrol trial. *J Crit Care,* 29**,** 374-9.

PENNING, S., LAMBERMONT, B., DESAIVE, T., PRETTY, C. G. & CHASE, J. G. 2014b. In silico assessment of a computerized model-based glycaemic control approach in a Belgian medical intensive care unit. *19th IFAC World Congress.* Cape Town, South Africa: IFAC (PapersOnline).

PENNING, S. M., LE COMPTE, A. J. P., MASSION, P. M. P., MOORHEAD, K. T. P., PRETTY, C. G. M., PREISER, J. C. M. P., SHAW, G. M. M. C., SUHAIMI, F. M., DESAIVE, T. P. & CHASE, J. G. P. 2012. Second pilot trials of the STAR-Liege protocol for tight glycemic control in critically ill patients. *Biomed Eng Online,* 11**,** 58.

PREISER, J. C., DEVOS, P., RUIZ-SANTANA, S., MELOT, C., ANNANE, D., GROENEVELD, J., IAPICHINO, G., LEVERVE, X., NITENBERG, G., SINGER, P., WERNERMAN, J., JOANNIDIS, M., STECHER, A. & CHIOLERO, R. 2009. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med,* 35**,** 1738 - 1748.

PRETTY, C. G., LE COMPTE, A. J., CHASE, J. G., SHAW, G. M., PREISER, J. C., PENNING, S. & DESAIVE, T. 2012. Variability of insulin sensitivity during the first 4 days of critical illness: implications for tight glycemic control. *Ann Intensive Care,* 2**,** 17.

ROOD, E., BOSMAN, R. J., VAN DER SPOEL, J. I., TAYLOR, P. & ZANDSTRA, D. F. 2005. Use of a computerized guideline for glucose regulation in the intensive care unit improved both guideline adherence and glucose regulation. *J Am Med Inform Assoc,* 12**,** 172-80.

SIGNAL, M., LE COMPTE, A., SHAW, G. M. & CHASE, J. G. 2012. Glycemic levels in critically ill patients: are normoglycemia and low variability associated with improved outcomes? *J Diabetes Sci Technol,* 6**,** 1030-7.

STEWART, K. W., PRETTY, C. G., TOMLINSON, H., THOMAS, F. L., HOMLOK, J., NOEMI, S. N., ILLYES, A., SHAW, G. M., BENYO, B. & CHASE, J. G. 2016. Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis. *Ann Intensive Care,* 6**,** 24.

UYTTENDAELE, V., DICKSON, J. L., SHAW, G. M., DESAIVE, T. & CHASE, J. G. 2017a. Untangling glycaemia and mortality in critical care. *Crit Care,* 21**,** 152.

UYTTENDAELE, V., DICKSON, J. L., SHAW, G. M., DESAIVE, T. & CHASE, J. G. 2017b. Virtual Trials of the NICE-SUGAR Protocol: The Impact on Performance of Protocol and Protocol Compliance. *IFAC-PapersOnLine,* 50**,** 6672-6677.

VAN DEN BERGHE, G., WILMER, A., HERMANS, G., MEERSSEMAN, W., WOUTERS, P. J., MILANTS, I., VAN WIJNGAERDEN, E., BOBBAERS, H. & BOUILLON, R. 2006a. Intensive Insulin Therapy in the Medical ICU. *N Engl J Med,* 354**,** 449-61.

VAN DEN BERGHE, G., WOUTERS, P., WEEKERS, F., VERWAEST, C., BRUYNINCKX, F., SCHETZ, M., VLASSELAERS, D., FERDINANDE, P., LAUWERS, P. & BOUILLON, R. 2001a. Intensive insulin therapy in critically ill patients. *N Engl J Med,* 345**,** 1359-67.

VAN DEN BERGHE, G., WOUTERS, P., WEEKERS, F., VERWAEST, C., BRUYNINCKX, F., SCHETZ, M., VLASSELAERS, D., FERDINANDE, P., LAUWERS, P. & BOUILLON, R. 2001b. Intensive insulin therapy in the critically ill patients. *N Engl J Med,* 345**,** 1359-1367.

VAN DEN BERGHE, G., WOUTERS, P. J., BOUILLON, R., WEEKERS, F., VERWAEST, C., SCHETZ, M., VLASSELAERS, D., FERDINANDE, P. & LAUWERS, P. 2003. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med,* 31**,** 359-366.

VAN DEN BERGHE, G., WOUTERS, P. J., KESTELOOT, K. & HILLEMAN, D. E. 2006b. Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. *Crit Care Med,* 34**,** 612-6.

WARD, L., STEEL, J., LE COMPTE, A., EVANS, A., TAN, C., PENNING, S., SHAW, G. M., DESAIVE, T. & CHASE, J. G. 2012. Interface Design and Human Factors Considerations for Model-Based Tight Glycemic Control in Critical Care. *Journal of Diabetes Science and Technology*, in-press.

WHITMORE, A., AGARWAL, A. & XU, L. D. 2015. The Internet of Things-A survey of topics and trends. *Information Systems Frontiers,* 17**,** 261-274.

WIENER, R. S., WIENER, D. C. & LARSON, R. J. 2008. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA,* 300**,** 933-44.